

# Circadian Rhythm and Sudden Death in Heart Failure

## Results from Prospective Randomized Amlodipine Survival Trial

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<b>OBJECTIVE</b>	The purpose of this study was to address the timing of sudden death in advanced heart failure patients.
<b>BACKGROUND</b>	Sudden death is a catastrophic event in cardiovascular disease. It has a circadian pattern prominent in the early AM, which has been thought to be due to a surge of sympathetic stimulation. We postulated that the distribution of events in advanced heart failure, with chronic sympathetic activation, would be more uniform implicating other potential mechanisms.
<b>METHODS</b>	We analyzed data from Prospective Randomized Amlodipine Survival Trial (PRAISE). Sudden deaths were analyzed by time of death in 4-h and 1-h blocks for uniformity of distribution in the entire cohort, and in the prespecified ischemic and nonischemic stratum. Further analyses were undertaken in the treatment groups of amlodipine and placebo, and among those receiving background therapy of aspirin and warfarin.
<b>RESULTS</b>	Sudden deaths in the overall cohort showed a nonuniform distribution with a PM peak but not an AM peak. The ischemic stratum also showed a PM peak, but sudden deaths within the nonischemic stratum were uniformly distributed. Neither amlodipine treatment nor aspirin or warfarin use altered the distribution.
<b>CONCLUSIONS</b>	Sudden death in advanced heart failure did not show an AM peak, suggesting that circadian sympathetic activation did not strongly influence these events. The PM peak noted is likely complex in origin and was not affected by antiischemic or antithrombotic medications. (J Am Coll Cardiol 2000;36:541-6) © 2000 by the American College of Cardiology

Sudden death occurs in all aspects of cardiovascular disease and our understanding of these events is limited. Large population studies have shown a nonuniform circadian distribution of events with a morning peak (1-3) and a smaller secondary afternoon peak (1,4). A similar circadian pattern has been noted with acute myocardial infarction (5,6), myocardial ischemia (7), out-of-hospital cardiac arrest (8), ventricular tachycardia post-myocardial infarction (9), and stroke (10). An explanation, particularly for the early peak, has been the coincidence of these events with evidence of activation of trigger factors relating to neurohormonal activation and thrombosis (2). Therefore, the concept has developed that neurohormonal activation leads to myocardial infarction, ischemia or lethal arrhythmias that can culminate in sudden cardiac death.

Sudden death is a major mode of death in patients with heart failure, varying between 20% and 75% of deaths depending on the definition and the studied population (11). However, triggers that might cause sudden death in

heart failure are uncertain in spite of the high prevalence, and only one study is available on the circadian pattern of events (12). Because the sympathetic nervous system is characteristically activated in heart failure, we postulated that this chronic neurohormonal stimulation would cause a more uniform distribution of sudden deaths that might aid in our understanding of these events. Therefore, we retrospectively analyzed the timing of sudden death within the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) (13) database to assess the distribution of events. Because the distribution might differ by the presence or absence of significant ischemic heart disease, we examined events within the prespecified strata for ischemic or nonischemic groups within PRAISE. Because medications with antiischemic or antithrombotic effects might also alter the distribution of events, we analyzed by treatment with the prospective study medication, amlodipine, as well as with aspirin and coumadin.

## METHODS

**Patient population.** The PRAISE trial was a randomized, double-blind, placebo-controlled study of amlodipine versus placebo treatment of 1,153 patients with advanced heart failure including left ventricular ejection fraction <30% and New York Heart Association (NYHA) class III or IV

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**Abbreviations and Acronyms**

ASIST	=	Atenolol Silent Ischemia Study
BHAT	=	Beta Blocker Heart Attack Trial
CASS	=	Coronary Artery Surgery Study
CAST	=	Cardiac Arrhythmia Suppression Trial
PRAISE	=	Prospective Randomized Amlodipine Survival Evaluation

symptoms. Patients on cardiac transplantation lists and beta-blocker agents were excluded from the study. Patients who had a history of myocardial infarction, angioplasty, bypass surgery, significant coronary artery disease or angina were clinically considered to have an ischemic etiology for their heart failure. The nonischemic category was used for all other patients. Other details of the patient population have been described (13). Patients were stratified by the etiology of the cardiomyopathy (ischemic or nonischemic) and then were randomized to receive either amlodipine or placebo.

**End points.** The primary end point of the PRAISE trial was the combined incidence of all-cause mortality or cardiovascular morbidity (hospitalization for at least 24 h for the following: sustained ventricular tachycardia or fibrillation, nonfatal myocardial infarction, pump failure requiring inotropic support or acute pulmonary edema). The secondary end point was all-cause mortality. An eight-member end point classification committee classified deaths in a cause-specific analysis using the following definitions. Sudden death was defined as death from cardiac or unknown causes that occurred instantaneously or within 60 min of symptom onset. Patients who were resuscitated from cardiac arrest, remained comatose and were pronounced dead within 72 h were classified as sudden deaths. Pump failure death was defined as progressive pump failure culminating in death, not associated with myocardial infarction or an observed sudden life-threatening arrhythmia. Death that occurred more than 60 min from the onset of symptoms during hospitalization for a proven myocardial infarction was classified as a fatal myocardial infarction.

Time of death was ascertained from available data including death certification, emergency medical forms, hospital records and investigator statements. Patients who did not have a time of death within 4 h were eliminated from analysis.

**Statistical analyses.** Baseline variables groups were compared for survivors and for sudden deaths. Statistical comparisons are for differences between groups. Circadian pattern for time of death was analyzed in six 4-h intervals. For example, a patient found dead at 2 AM and last seen at 10 PM would have 0.25 assigned to each hour in that interval. The four blocks were then tested for uniformity using a chi-square analysis. These analyses were undertaken for the entire cohort of sudden death, ischemic and nonischemic strata, treatment with amlodipine and placebo and treatment with aspirin or coumadin. Due to concern that the 4-h interval analysis may have introduced bias, we analyzed also by 1-h intervals using a chi-square analysis for uniformity.

**RESULTS**

Overall, there were 352 deaths among the 1,153 patients in PRAISE. The Endpoint Classification Committee determined 185 to be sudden deaths. Patient characteristics for sudden death and survivor patient groups are seen in Table 1. The survivor patients were less commonly class IV, ischemic etiology or with a previous history of myocardial infarction than the patients who died suddenly.

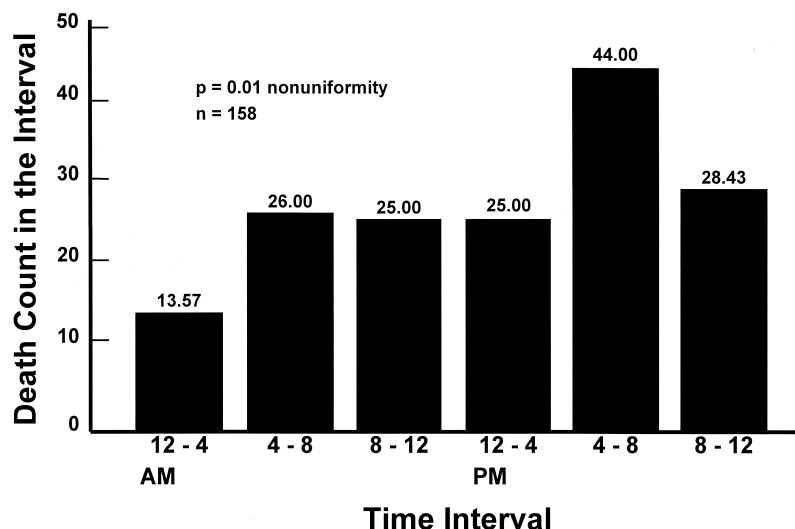
**Circadian analysis.** Of the 185 sudden death patients, a time of death could be determined within a 4-h interval in 158 (85.4%) (Fig. 1). Testing for circadian distribution with a chi-square analysis, using 4-h blocks, indicated a nonuniformity ( $p < 0.01$ ) with a striking peak at the 4 PM to 8 PM interval (Fig. 1). An early AM peak was not observed. Analysis of the prespecified ischemic and nonischemic strata indicated that nonuniformity was present in the ischemic patients ( $p < 0.001$ ) with a peak in the 4 PM to 8 PM interval, but not in the nonischemic group (Fig. 2).

Analysis of events was also undertaken by 1-h intervals.

**Table 1.** Selective Baseline Characteristics of Survivors and Sudden Death Patients

	Measure	Alive	Sudden Death + Post.R
Age (yrs)	N	740	162
	Mean	64 (23.4–93.7)	64.7 (–5.4–93.7)
Cardiothoracic ratio	N	680	142
	Mean	0.6 (0.2–0.9)	0.6 (0.2–0.9)
LVEF (%)	N	740	162
	Mean	21.2 (5.0–65.0)	20 (7.0–30.0)
Baseline covariate			
Baseline NYHA classification	Percent class IV	15.15	27.16
Baseline etiology	Percent ischemic	59.19	66.67
History of MI	Percent yes	56.35	66.05
History of diabetes	Percent yes	35.68	39.51
History of hypertension	Percent yes	58.78	53.70
Gender	Percent female	26.08	16.67

LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.



**Figure 1.** All sudden deaths graphed by 4-h intervals. Analysis includes those with 4-h interval time of death with partial count included for each hour of the interval.

The data are limited by the number of events within each interval but a trend for nonuniformity was present for the entire cohort of sudden deaths with a PM peak ( $p = 0.08$ ) (Fig. 3). A similar nonuniform distribution was noted within the ischemic group ( $p = 0.005$ ).

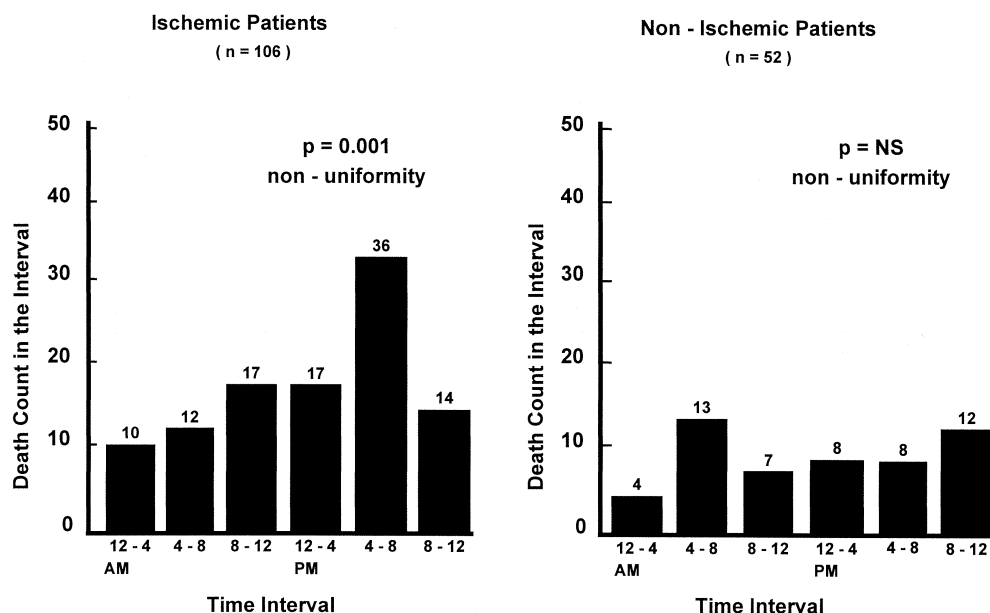
A minority of patients experiencing sudden death had documented heart rhythm data. For those with ventricular tachycardia or ventricular fibrillation, nonuniformity was weakly seen ( $p = 0.046$ ) with a PM peak, while a nonuniform distribution was not seen for other rhythms (Fig. 4).

**Treatment effect.** The prospective treatment in PRAISE was amlodipine, a calcium antagonist with antiischemic properties. Patients treated with amlodipine showed a similar distribution of events to the overall cohort in analysis of 4-h intervals ( $p = 0.005$ ). Amlodipine treatment did not

alter the distribution of events either in the entire sudden death cohort or within the strata. Antithrombotic medications commonly used in PRAISE were warfarin and aspirin. Both were associated with the same pattern of nonuniformity in the ischemic strata: warfarin ( $p = 0.0002$ ) and aspirin ( $p = 0.03$ ).

## DISCUSSION

The current study evaluated the circadian pattern of sudden death in advanced heart failure patients. The major findings were that events did not cluster in the AM but did later as a PM peak. This PM cluster of events was present only in ischemic cardiomyopathy patients and was not altered with antiischemic or antithrombotic treatment.



**Figure 2.** Sudden death in the ischemic and nonischemic strata with time of death within 4-h intervals.

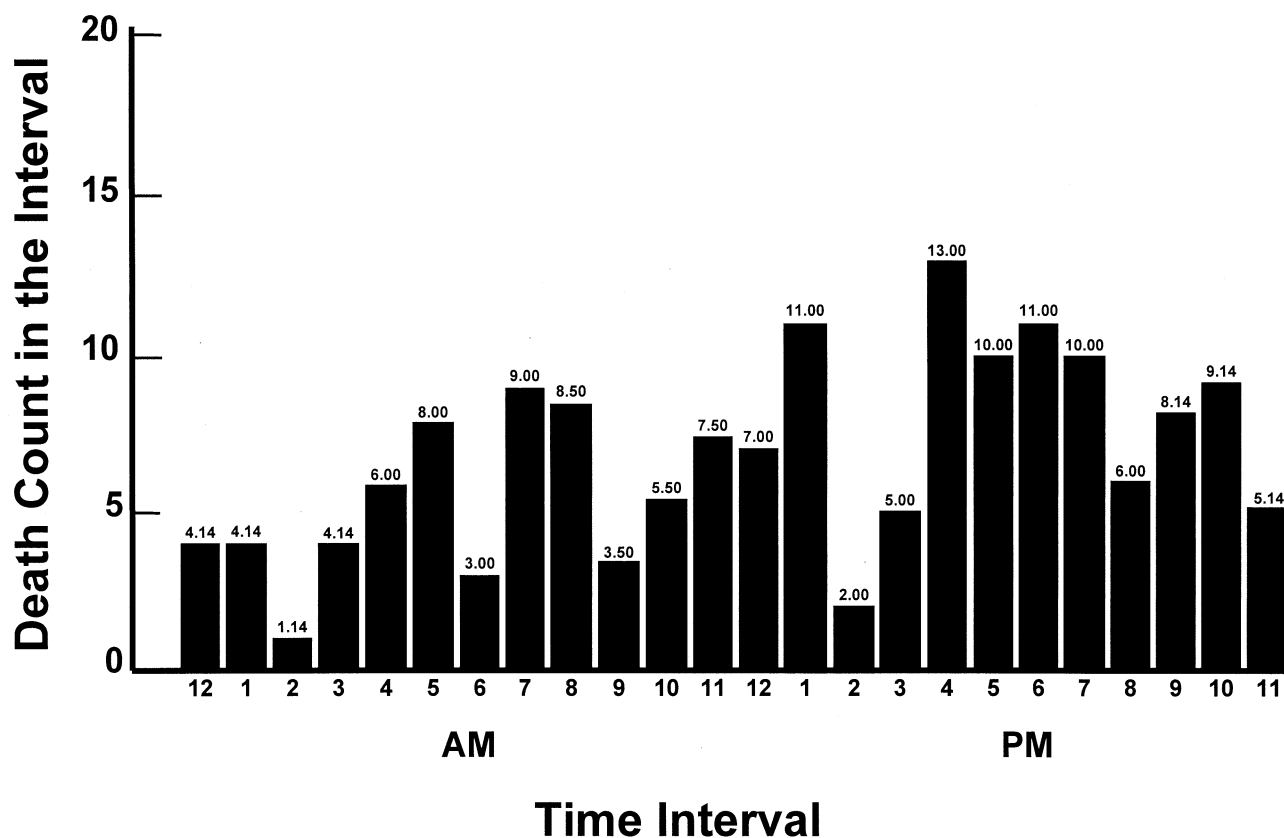


Figure 3. All sudden deaths with time of death within 1-h intervals.

**Circadian rhythm and myocardial events.** The PRAISE results differ from previous reports that demonstrated a single peak in early morning or a bimodal distribution of deaths in morning and late afternoon or evening. In 1987 Muller *et al.* (1) reported data that sudden death incidence was highest between 7 AM and 11 AM, while Willich *et al.* (2) reported a peak between 7 AM

and 9 AM. While both reports were from large unselected databases, other groups have published data with similar results in heart failure (12) and in the elderly (14). Of interest, Arntz *et al.* (15) reported that while a bimodal pattern was prominent in those over age 65, older patients had only a monophasic peak. Therapy also can alter the pattern. In CAST, Peters *et al.* (16) noted a

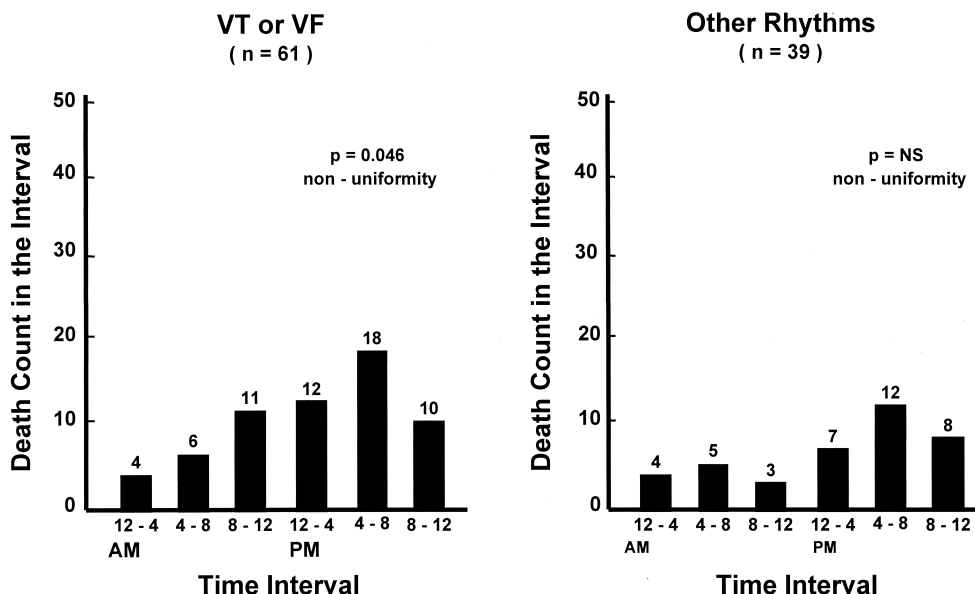


Figure 4. All sudden deaths with a presenting identifiable rhythm. (A) Ventricular tachycardia or fibrillation; (B) other rhythms.

biphasic pattern in placebo patients but an early AM peak only in the antiarrhythmic group.

A circadian pattern of myocardial infarction and myocardial ischemia has paralleled the pattern of sudden death and suggested a possible relation. Muller et al. (4) in 1985 reported a peak of myocardial infarction from 6 AM to 12 noon. Other reports, however, indicate that a bimodal distribution of events occurs. Hjalmeren et al. (5) reported a bimodal peak of events for 6 AM to 12 noon and 6 PM to 12 midnight, although only a PM peak in heart failure patients. Myocardial ischemia has been noted also to follow a circadian pattern of early AM peak incidence in recent reports (7,17). Other myocardial events, particularly ventricular tachycardia post-myocardial infarction (9) and out-of-hospital cardiac arrest (8), have also shown a circadian distribution. The current study does show a limited circadian pattern for sudden death with ventricular arrhythmic events but not other rhythms. Similar findings were noted by Arntz et al. (15) in a nonselected population.

The PRAISE data do conflict with the report of Moser et al. (12) in which sudden deaths in a heart failure population peaked between 6 AM and 12 noon. The patient databases were both that of advanced heart failure. However, the larger PRAISE population was older (64 vs. 48 years) and more commonly on a converting enzyme inhibitor (100% vs. 40%) or digitalis (100% vs. 50%). The sudden death population in PRAISE was also predominantly ischemic heart failure (63% vs. 43%). Furthermore, the distribution of events may have been further altered by cardiac transplant in the Moser study (31% vs. 1.5% in PRAISE). Finally, methodologic factors such as sudden death definitions or adjudication may also differ in a single center analysis (such as Moser et al. [12]) compared with a multicenter trial with a central end points committee as in PRAISE.

**Relation of mechanism.** It should be emphasized that sudden death in heart failure is a topic of great complexity. While the events are often ascribed to ventricular tachycardia or ventricular fibrillation, Luu et al. (18) demonstrated that a minority of sudden terminal events were tachyarrhythmias. Undiagnosed myocardial infarction is of particular interest due to the similarity between sudden death and myocardial infarction circadian events patterns in previous reports. The finding, in this analysis, that the PM peak is only present in the ischemic stratum is concordant with other lines of evidence implicating ischemic events as a mechanism of sudden death. In non-heart failure populations, based on the prevalence of coronary thrombus on autopsy and of proven myocardial infarction in cardiac arrest survivors, Willich et al. (2) estimated that a third of sudden deaths in the general population may be due to myocardial infarction. Retrospective data from CASS (19) in angina patients and uncontrolled data on cardiac arrest patients (20,21) also support an ischemic etiology because sudden death appears to be decreased by coronary bypass revascularization grafting. Further, autopsy data from ATLAS (22), while likely influenced by selection bias, is intriguing

in showing strong evidence of acute ischemic events among sudden deaths in ischemic cardiomyopathy patients.

Adrenergic activation has been a suspected trigger for sudden deaths and ischemic events because the AM peak corresponds to the time in which awakening most commonly occurs. This awakening prompts increased sympathetic activation, which in turn affects heart rate, vasoactivity and the clotting cascade, which then could precipitate ischemic episodes (23-27).

While the direct relation of ischemic triggers to cardiovascular events remains somewhat speculative, agents that effect them have altered the circadian distribution of events. Beta-blocker therapy has been noted to decrease the morning peak of myocardial ischemia in ASIST (28) and of sudden deaths in BHAT (29). Parker et al. (30) also noted that beta-blockers decreased episodes of ischemia associated with awakening and physical activity. Curiously, PM episodes were less likely to involve heart rate rises and were less influenced by beta-blockade. Aspirin therapy has also been associated with a decrease in morning myocardial infarction presumably by its effect on platelet aggregability (6).

The role for an adrenergic trigger in heart failure as an explanation for a circadian rhythm of events is more difficult. Advanced heart failure patients have chronically elevated catecholamines levels (31), which are at once both markers for disease severity as well as toxic substances (32). The sustained catecholamine levels produce deception downregulation and desensitization (33). Furthermore, while direct measurements of circadian sympathetic activation are lacking, indirect measurement such as heart rate variability indicates little change in low-frequency oscillations that are influenced by change in sympathetic tone in heart failure (34). Heart failure patients would then be less likely to have heart rate-driven ischemic events, such as those described by Parker et al. (30) because heart rate would likely change little and episodic adrenergically driven events would be rare. A chronically stimulated adrenergic state would then cause a uniformly increased risk for events. Hence, the lack of an early morning peak is unsurprising. Other populations, where the effect of an alteration in sympathetic time is blunted such as diabetics with severe autonomic dysfunction (35), or patients on a beta-blocker (29), also lack a morning peak.

The late afternoon peak found in the current study has no clear explanation, but the finding that the PM circadian pattern is only present in the ischemic stratum raises the possibility that some portion of these events could be ischemic. However, in PRAISE, medications with antiischemic properties such as amlodipine or antithrombotic properties such as aspirin or warfarin did not alter the distribution of events. Previously Ridker et al. (6), with aspirin, and Parker et al. (30), with beta-blockers, had also shown no effect on the PM peak, suggesting that this phenomena may be a complex interaction between multiple factors leading to sudden death.



**Limitations.** The current analysis was a retrospective analysis within the PRAISE database. As discussed above, the assessment of sudden death is complex and often indicates a mode rather than a specific mechanism. The PRAISE end points committee carefully adjudicated deaths using conventional prospective definitions similar to other trials. The time of death could be estimated to within 4 h in 82% of sudden death patients, which compares favorably with other study populations: CAST 78% (16) and Moser 75% (12). This analysis does not contain data on time of awakening. However, Peters et al. (16) noted little relation of awakening to events in the CAST placebo group and the persistence of the PM peak even when adjusted for weakening peak.

**Clinical implications.** The circadian analysis from PRAISE does not support the finding in other populations of an AM peak of sudden deaths. The episodic sympathetic activation in other populations that do not have chronic adrenergic stimulation may not be relevant in heart failure patients. The PM peak was not altered by antiischemic or antithrombotic agents and therefore may be a complex interaction of risk factors. Because heart failure patients die suddenly in nearly half of fatal events, further analysis is needed to assess this crucial area.

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